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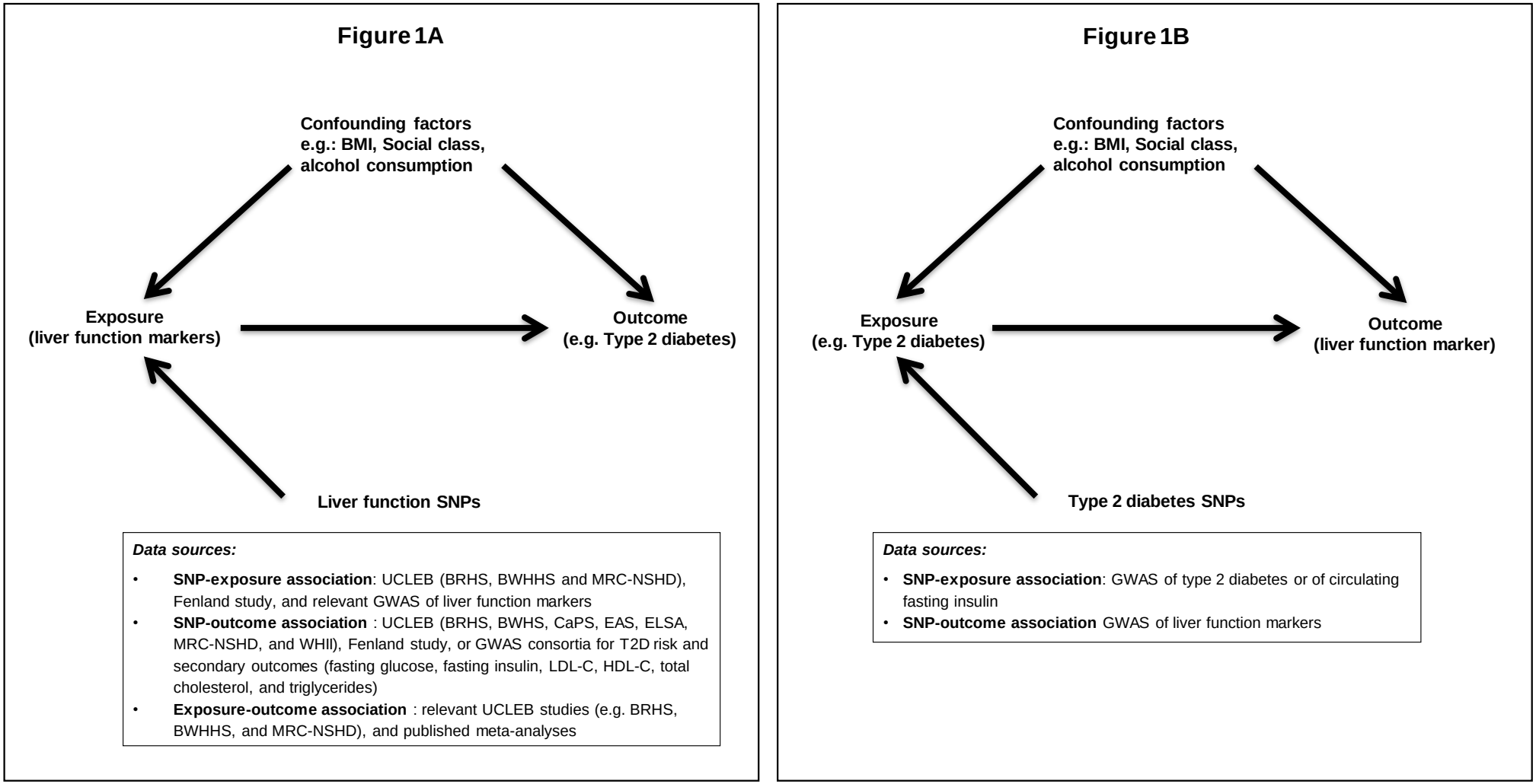

Figure 1. Study design and data sources used to investigate the effect of liver dysfunction (proxied by biomarkers: ALT, AST, ALP, and GGT) on type 2 diabetes or secondary outcomes (fasting glucose, fasting insulin, LDL-C, HDL-C, total cholesterol, and triglycerides) (**Figure 1A**) and the effect of predisposition to type 2 diabetes or insulin resistance on circulating liver function biomarkers (**Figure 1B**)

As shown in **figure 1A**, the multivariable association of liver function markers with T2D risk (or related outcomes) was estimated by meta-analysing results from each data source using logistic regression models (or linear regression models in the case of secondary outcomes) with participant-level data from relevant studies within UCLEB consortium (BRHS, BWHHS, MRC-NHSD) and summary-level data from the published meta-analyses of Kunutsor *et al* (2013) and Fraser *et al* (2009). We also estimated the association of liver function markers with T2D risk (or secondary outcomes) using a Mendelian randomization approach. In Mendelian randomization analysis, we used different data sources to estimate the SNP-liver function marker association (UCLEB consortium — BRHS, BWHHS and MRC-NHSD —, Fenland study, and GWAS of liver function markers — Chambers *et al* (2011)) —, and SNP-T2D risk association (UCLEB — BRHS, BWHS, CaPS, EAS, ELSA, MRC-NHSD, and WHII —,

and GWAS consortium) or SNP-secondary outcomes. As shown in **figure 1B**, the summary-level data for the association of SNP-T2D risk and SNP-fasting insulin for the reverse MR was extracted from GWAS consortia, and the association of SNP-liver function marker was extracted from Chambers *et al* (2011). ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BRHS: British Regional Heart Study; BWHHS: British Women's Heart and Health Study; CaPS: Caerphilly Prospective Study; DIAGRAM consortium: Diabetes Genetics Replication And Meta-analysis consortium; EAS: Edinburgh Artery Study; ELSA: English Longitudinal Study of Ageing; GGT: gamma-glutamyl transferase; GWAS: genome-wide association study; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; MRC-NSHD: National Survey of Health and Development; SNPs: single nucleotide polymorphisms; T2D: type 2 diabetes; UCLEB consortium: UCL-LSHTM-Edinburgh-Bristol consortium; WHII: Whitehall II study.